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Title: Risk of Heart Failure in Obese Patients with and Without Bariatric Surgery in Sweden – a Registry-Based Study

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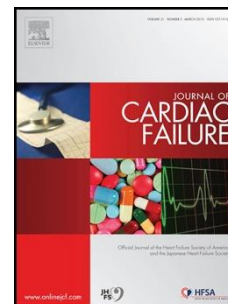
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# Risk of heart failure in obese patients with and without bariatric surgery in Sweden – a registry-based study

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### Highlights

- Among obese patients, bariatric surgery conferred a lower risk of heart failure
- Heart failure was less than half of non-surgical obese patients
- Bariatric surgery could prevent heart failure in the severely obese

### Abstract

**Background:** Obesity is a known risk factor for heart failure. The prevalence of both conditions has increased in Sweden the last decades. Obesity surgery has been shown to improve cardiac function. We therefore investigated whether the risk of heart failure was lower in obese patients after bariatric surgery compared with obese patients without surgical intervention.

**Methods and results:** From the Swedish National Patient Registry we created a cohort including 47,859 patients aged 18-74 years with a primary diagnosis of obesity from 2000 to 2011. Of these, 22,295 (46.6%) underwent bariatric surgery (mean age 40.7 (standard deviation (SD) 10.7) years, 75.9% female). There were 25,564 (53.4%) non-surgical obese patients (mean age 44.3 (SD 13.2) years, 66.8% female). Patients who underwent bariatric surgery had a markedly reduced risk of heart failure compared with non-surgical obese patients (age and sex adjusted hazard ratio (HR) 0.37, 95% confidence interval (CI) 0.29-0.46). The lower risk persisted after further adjustment for baseline differences in known risk factors for heart failure (HR 0.37, 95% CI 0.30-0.46). **Conclusion:** Patients who underwent bariatric surgery had a reduced risk of heart failure after surgery compared with non-surgical obese patients.

**Keywords:** Heart failure, obesity, bariatric surgery, mortality, epidemiology

## Introduction

Heart failure is a major public health problem, with an estimated lifetime risk of 1 in 5 among men and women in the United States.<sup>1</sup> The prevalence of heart failure is approximately 1–2% in the adult population in developed countries,<sup>2</sup> and it is a leading cause of hospitalization, morbidity, and mortality among the older population ( $\geq 65$  years)<sup>3</sup>. Recent data indicate that the incidence of heart failure is increasing among people younger than 45 years in Sweden.<sup>4</sup>

Obesity is increasingly being recognised as a major risk factor for heart failure.<sup>5, 6</sup> A recent study demonstrated a strong association between adolescent body mass index (BMI) and early heart failure<sup>7</sup> and indicated a potential association between the increased prevalence of obesity<sup>8</sup> and rising rates of heart failure among younger individuals.<sup>4, 9</sup> The prevalence of morbid obesity has more than doubled worldwide during the last few decades. In Sweden, the prevalence of obesity in 2013 was estimated at 19.8% in women and 18.9% in men at least 20 years old.<sup>10</sup> The effects of obesity on the cardiovascular system are likely partly mediated by increased blood pressure and increased levels of glucose and lipids.<sup>11</sup>

Bariatric surgery is currently the only available treatment with documented sustained weight loss and significant improvement or complete resolution of obesity-related comorbidities in morbidly obese patients.<sup>12</sup> During the 2000s, gastric bypass became the most commonly performed procedure for bariatric surgery in Sweden and worldwide. Although the sleeve gastrectomy procedure rose in popularity during 2008 and is the most performed procedure in some countries,<sup>13</sup> to date gastric bypass is still the most commonly performed procedure in Sweden.<sup>14</sup> Bariatric surgery, and gastric bypass in particular, improve the prognosis for morbidly obese patients as these procedures decrease cardiovascular risk by improving blood pressure, blood lipid levels, and dysglycemia.<sup>15, 16</sup> A report from the

Scandinavian Obesity Surgery registry (SOReg) showed that patients who had undergone bariatric surgery in Sweden from 2007 to 2012 had an average BMI of 45 when they underwent the operation. During the first year after surgery, their weight stabilised at an average BMI of around 32. After the procedure, the patients initially kept their weight stable and slowly started gaining weight 5 years later.<sup>14</sup> Given the strong association between BMI and heart failure,<sup>5</sup> this weight reduction should, in theory, decrease the risk of heart failure, as shown in a recent study where bariatric surgery patients were compared to a selected group of obese patients participating in an intervention program.<sup>17</sup>

In the present study, we aimed to test the hypothesis that the risk of hospitalization for heart failure and overall mortality would decrease among patients who have undergone bariatric surgery, compared with patients with an obesity diagnosis who have not undergone such surgery in a large cohort with long-term and near complete follow-up.

## Methods

### Study design

In this nationwide observational Swedish cohort study, data from the Swedish National Patient Registry was used to obtain information about obesity diagnosis, comorbidities, and bariatric surgery. The Patient Registry includes records for all hospitalizations and specialist outpatient visits in Sweden since 2001, with complete data for principal and contributory discharge diagnoses for all patients since 1987.<sup>16</sup> The registry, in general and for bariatric surgery and heart failure diagnosis specifically, has validity of 85–95% when compared with patient records.<sup>16–18</sup> In addition, the Cause of Death Registry, which documents underlying causes of all deaths among Swedish residents, was linked with the Patient Registry through the Swedish 10-digit personal identification number to collect date and causes of death. All data were anonymized. The Regional Ethical Review Board in Stockholm approved this study.

### Study cohort

From the Patient Registry, we created a cohort that included all patients from 18 to 74 years old with a first recorded principal diagnosis of obesity in Sweden. The International Classification of Disease (ICD) version 10, which has been used in Sweden since 1997, was used to identify patients with a principal diagnosis of obesity, defined by the codes E65, E66, or E68. The inclusion started at first recorded diagnosis of obesity between January 1, 2000 and December 31, 2011. The patients were then followed up until the time of first hospital discharge with a heart failure diagnosis (principal or contributory), death, or the end of follow up (December 31, 2012), whichever occurred first. All patients with a prevalent diagnosis of heart failure (codes 428 for ICD9 and I50 for ICD10) at or prior to their obesity diagnosis was

excluded from the study (n=853). We also excluded patients who died on the same day that they were diagnosed with obesity (n=4).

The Swedish Classification of Operations and Major Procedures was used to identify patients who had undergone bariatric surgery: operation codes JDF00, JDF01 (vertical banded gastroplasty), JDF10, JDF11 (gastric bypass), JDF20, JDF21 (gastric banding), JFD03, and JFD04 (duodenal bypass). Two patients with bariatric surgery codes who did not have a principal diagnosis of obesity were excluded. In bariatric surgery patients who had an obesity diagnosis but the date of diagnosis was missing (n=67), the date of surgery was used as the inclusion date. For patients who had obtained their first principal diagnosis of obesity at the same day as their bariatric surgery, we used the secondary diagnosis of obesity closes in time prior to surgery.

### **Definition of heart failure and comorbidities**

The main outcome was first heart failure diagnosis in any position in the Patient Registry. We defined heart failure by the ICD10 code I50. Baseline comorbidities were defined as any of the following diagnoses prior to or concomitant with the index obesity diagnosis: hypertension (ICD9: 401–405; ICD10: I10–I15), diabetes (ICD9: 250; ICD10: E10–E14), sleep apnea (ICD9: 327.2, 780.5; ICD10: G47.3), coronary heart disease (ICD9: 410–414; ICD10: I20–I25), malignancy (ICD9: 140–208; ICD10: C00–C97), myocardial infarction (ICD9: 410; ICD10: I21), atrial fibrillation (ICD9: 427D; ICD10: I48), stroke (ICD9: 431–434, 436; ICD10: I61–I64), valvular disease (ICD9: 394–398, 745–747; ICD10: I05–I09, I33–I39, Q20–Q28, Q87, Q89), or cardiomyopathy (ICD9: 425; ICD10: I42, I43).



## Statistical analysis

Chi-square tests were used to determine differences in mean values between non-surgical and surgical patients at obesity diagnosis and date of bariatric surgery. The absolute risk of heart failure and death were estimated and illustrated with a multi-state disease model (figure 1) where outcome is dependent on a patient's previous health state. All patients started at the first state, obesity diagnosis, from there, the transition probability of moving from one state to another was estimated with two Cox proportional hazard regressions, to assess the relative risk of heart failure and mortality over time for obese surgical compared with obese non-surgical patients. The covariates in our first model were age and sex. In the second model, we added history of coronary heart disease, hypertension, and diabetes. Age was entered as a continuous variable in both models. In addition, we stratified the models by the age groups 18–44, 45–59, and 60–74, and comorbidity at baseline. The covariates satisfied the assumption of proportional hazards.

Incidence rates for heart failure and death were calculated as the ratio of events and person-years of follow-up for all patients. Person-time in the non-surgical group was calculated from obesity diagnosis until first event of bariatric surgery, heart failure, death or end of study. Person-time in the surgical group was calculated from date of bariatric surgery first event of heart failure, death, or end of study. The rates were calculated for the age groups 18–44, 45–49, 50–54, 55–59, 60–64, 65–69, and 70–74 years, categorized from the age at obesity diagnosis. Survival probability for heart failure were estimated according to the Kaplan-Meier method.

All statistical analyses were performed using the statistical software SAS, version 9.4 (SAS Institute, Cary, NC).

## Results

### Baseline data

The study cohort included 47,859 patients from 18 to 74 years old with a principal diagnosis of obesity (mean age at obesity diagnosis 42.6 years; standard deviation (SD) 12.2 years). Of these, 22,295 (46.6%) had bariatric surgery. The mean age at obesity diagnosis was 40.7 (SD 10.7) years in the surgical group and 44.3 (SD 13.2) years in the non-surgical group (Table 1). Most patients were women (75.9% in the surgery group and 66.8% the non-surgery group). The median time from obesity diagnosis to bariatric surgery was 0.7 (interquartile range (IQR) 1.4) years.

Hypertension and diabetes were the most commonly recorded comorbidities as 26% of the men and 13.5% of the women had hypertension, and 16.8% and 9.3% respectively had diabetes at date of obesity diagnosis (Table 1). At the time of bariatric surgery 32.9% and 18.1% of men and women, respectively, had hypertension and 23.2% and 12.3%, respectively, had diabetes (Supplementary table 1). At obesity diagnosis, 8.0% of the men had a recorded diagnosis of coronary heart disease, compared with 5.1% at the time of surgery. Few patients (<5%) in any of the groups had a recorded diagnosis of cancer, myocardial infarction, atrial fibrillation, stroke, congenital heart disease, valve disease, or cardiomyopathy (Table 1).

Of the surgical patients, 20,680 (92.8%) underwent gastric bypass surgery, and 84.1% of these had laparoscopic procedures. The remaining surgical patients underwent gastric banding (n=772, 3.5%), vertical banded gastroplasty (n=678, 3.0%), or gastro-duodenal bypass (n=165, 0.7%).

### Incidence of heart failure

There were 1033 patients hospitalized with heart failure, including 944 (3.7%) in the

non-surgical group and 89 (0.4%) in the surgical group. The median follow-up time for all cohort members from diagnosis of obesity to heart failure was 3.7 (IQR 3.2) years. The overall incidence rate of heart failure was 5 times higher among the non-surgical patients (6.9/1000 person-years, 95% CI 6.4–7.3), than among the surgical patients (1.0/1000 person-years, 95% CI 0.8–1.3). The incidence rate increased with age in all participants, from 1.5/1000 person-years (95% CI 1.2–1.8) to 39.9/1000 person-years (95% CI 32.6–47.4) among 18–44 and 70–74 year old non-surgical patients, respectively, and from 0.3/1000 person-years (95% CI 0.1–0.4) to 10.6/1000 person-years (95% CI 1.3–19.9) among 18–44 and 65–69 year old surgical patients, respectively (there were no cases in the oldest age group) (Table 2).

### **Mortality rate**

The median follow-up time from obesity diagnosis to death for the entire cohort was 3.8 (IQR 3.2) years. There were 1189 (2.5%) deaths, 938 (3.7%) of which occurred among the non-surgical patients (5.5% of the men and 2.7% of the women) and 251 (1.1%) among the surgical patients (1.8% of the men and 0.9% of the women). Twenty-one of the surgical patients died within 30 days of operation due to obesity (n=17), unknown cause (n=2), incisional hernia (n=1), or myocardial infarction (n=1). The mortality rates were higher among the non-surgical patients (6.7/1000 person-years, 95% CI 6.3–7.1) than the surgical patients (2.9/1000 person-years, 95% CI 2.6–3.3) (Supplementary Table 2).

### **Overall risk of heart failure and mortality**

The risk of heart failure was lower among patients who underwent bariatric surgery compared with the obese patients who did not have such surgery (Figure 1). The age and sex adjusted Cox regression analysis showed a 63% lower risk of heart failure (HR 0.37, 95% CI

0.29–0.46). In the full model, which adjusted for baseline differences in known risk factors for heart failure, the decreased risk among the surgical patients remained unchanged (HR 0.37, 95% CI 0.30–0.46). The decreased risk persisted in all age groups. Cases without known diabetes at baseline and who underwent bariatric surgery had the lowest risk of heart failure (HR 0.26, 95% CI 0.16–0.42). The risks for patients with hypertension or coronary heart disease were similar to those without these diseases at baseline (Figure 2).

The risk of overall mortality was lower among the surgical patients. The Cox regression analysis showed a 22% reduced risk of mortality (sex and age adjusted model: HR 0.78, 95% CI 0.67–0.90; full model: 0.78, 95% CI 0.68–0.90) (Figure 2).

Overall, heart failure free survival 12 years after baseline was higher in the surgical group (Survival probability 0.98) compared to the surgical group (survival probability 0.93). The difference in survival started to deviate directly after baseline.

## Discussion

In this nationwide Swedish cohort study, we found that patients who underwent bariatric surgery had substantially lower risk of developing heart failure and lower mortality compared with non-surgical obese patients.

The incidence of heart failure depends on the criteria used to define heart failure. Studies which included patients treated in primary care showed higher incidence rates than studies based on hospitalizations only.<sup>21 22</sup> A recent study from our group, which included hospitalized cases only, found that heart failure rates were about 0.5 per 1000 person-years in persons aged 45–54.<sup>4</sup> In the present study, we found rates that were 2–3 times higher, even in the bariatric surgery group. This indicates that the risk of developing heart failure in obese patients after bariatric surgery may still be substantially higher than in the general population.

One recent study which identified patients from the SOReg over the period 2007-2012 and compared them with obese subjects participating in an intervention program showed that bariatric surgery patients had a 54% reduced risk of heart failure.<sup>17</sup> Although based on a later inclusion period, the patients in the surgery group comprised the same patients as our study population for the corresponding years. The risk reduction was less marked than in our analysis, likely due to weight loss in the control population after participation in the intervention program, whereas the non-surgical obese in our study probably did not lose weight to the same extent. Accordingly, these two studies represent a continuum from non-surgical obese, with weight loss that was likely minimal, to moderate weight loss with lifestyle intervention, and marked weight loss with surgery, and successively lower risk of heart failure, strengthening the causal role of obesity in the development of heart failure. Another study with long follow-up showed that bariatric surgery prevented cardiovascular events in surgical obese patients compared with non-surgical obese controls.<sup>23</sup> This decrease in overall cardiovascular risk could be explained by an improvement in cardiac structure and

function through improvements in type 2 diabetes and hypertension.<sup>24</sup> As these comorbidities are known risk factors for heart failure,<sup>5</sup> it is a plausible explanation for the lower risk seen in the present study. Another potential explanation for this risk reduction is the decrease in body weight *per se* following bariatric surgery. Previous studies have demonstrated that an elevated BMI is associated with an increased risk of developing heart failure.<sup>5, 6</sup> This is particularly true in younger individuals. Among 18-year-old males, those with BMI  $\geq 35$  had an almost 10-fold increased risk for early heart failure compared with those with a BMI around 20.<sup>7</sup> In addition, weight loss after bariatric surgery has been reported to reverse the disturbances in left ventricular function.<sup>25</sup> We know from previous reports that surgical obese patients in Sweden during the time period for the present study lost a substantial amount of excess weight post-surgery,<sup>14</sup> while we have good reason to believe that the weight of the non-surgical obese patients remained stable.<sup>26, 27</sup>

Overall mortality was lower among those who underwent bariatric surgery compared with those who did not. This result is consistent with previous studies.<sup>27, 28</sup> In addition, the absolute risk of mortality within one year of bariatric surgery has been found to be low,<sup>29</sup> which is consistent with this study. There were few deaths within 30 days after bariatric surgery. The inclusion of those deaths in the analysis did not change the risk estimates.

### Strengths and limitations

A major strength of this study was that we were able to include almost all patients in Sweden who underwent bariatric surgery during the study period. This provided a large study population and a long follow-up period (up to 12 years in some cases). Additionally, we were able to identify a similar group of patients with obesity as the primary diagnosis in the Patient Registry for comparison. The large number of heart failure cases, using complete and valid Swedish hospitalization data, is another advantage of this study.<sup>18, 19</sup> Finally, we only included

patients with a primary diagnosis of obesity in this study, which was more likely to capture patients actively seeking help for their obesity or obesity related problems and not those who received their obesity diagnosis in conjunction with hospitalization for other conditions. If patients with secondary diagnosis of obesity were to be included, the cohort would include many patients who would never be considered for bariatric surgery due to their older age and severe comorbidity.

There are also a number of limitations, including the fact that we had no anthropometric data. However, these data are available from other studies.<sup>14</sup> In the Swedish Obese Subjects (SOS) trial,<sup>27</sup> surgical cases had a BMI of about 42 kg/m<sup>2</sup>, with about 2 units lower for non-surgical cases. Another limitation is the lack of information about the severity and type of heart failure, including echocardiography or ejection fraction, or whether the index hospitalisation was due to acute decompensated heart failure, or worsening of heart failure already diagnosed in a primary care setting. It could be hypothesized that the patients with an obesity diagnosis who underwent bariatric surgery were overall healthier and may have had less severe heart failure, which did not result in hospitalization, compared with other obese patients. In addition, patients underwent bariatric surgery when they were relatively young and few of them were at an age where heart failure usually occurs. Furthermore, even though we adjusted for major comorbidities, this information might have been incomplete, as the adjustments did not alter the relative risk of heart failure, leaving a risk of residual confounding. Moreover, other dimensions of patients' characteristics, which lead to the decision to operate, remained unknown to us. These included psychological factors, fear of surgery, willingness to undergo a major operation, and the surgeon's perception of the patient's suitability for any of these procedures. This introduced a risk of selection bias. However, it would be difficult to explain the markedly lower risk in the surgical group solely by these methodological issues.

## Conclusions

This nationwide Swedish cohort study showed that patients who underwent bariatric surgery had a markedly reduced risk of developing heart failure compared with non-surgical obese patients. The incidence rate of heart failure for a non-surgical obese patient was almost 5 times higher than for an obese patient who underwent bariatric surgery. This suggests that bariatric surgery could prevent heart failure in severely obese patients. More data are needed on characteristics in obese persons selected for surgical or non-surgical management before a firm conclusion on the effectiveness of surgery for the prevention of heart failure can be made.

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**Conflict of Interest:** none declared.



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Accepted Manuscript

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Figure 1. Multi-states disease model showing the absolute risk of moving from one state to another. 1= Obesity diagnosis to bariatric surgery, 2= Obesity diagnosis to heart failure, 3= Obesity diagnosis to death, 4= Bariatric surgery to heart failure, 5= Bariatric surgery to death, 6= Survival, free of heart failure at end of study.

Figure 2. Hazard ratios for risk of heart failure and mortality comparing patients with obesity who did and did not undergo bariatric surgery.

Figure 3. Heart failure free survival by operation and non-operation.

**Table 1. Age distribution at obesity diagnosis and comorbidities at for all at obesity diagnosis, among non-surgical patients at obesity diagnosis, and among surgery patients at date of surgery**

	<b>Total</b>	<b>Non-surgical</b>	<b>Surgical</b>	
<b>All</b>	<b><i>n</i>=47,859</b>	<b><i>n</i>= 25,564</b>	<b><i>n</i>= 22,295</b>	
(% of total)	(100%)	(53.4%)	(46.6%)	
Age years SD	42.6±12.2	44.3±13.2	40.7±10.7	
18-44 <i>n</i> (%)	27,488 (57.4)	13,139 (51.4)	14,349 (64.3)	
45-54 <i>n</i> (%)	11,280 (23.6)	5939 (23.2)	5341 (24.0)	
55-74 <i>n</i> (%)	9091 (19.0)	6486 (25.4)	2605 (11.7)	
<b>Comorbidities</b>				<b>p*</b>
Hypertension <i>n</i> (%)	6892 (14.4)	4557 (17.8)	4830 (21.7)	<.0001
Diabetes mellitus <i>n</i> (%)	4925 (10.3)	3010 (11.8)	3325 (14.9)	<.0001
Sleep apnea <i>n</i> (%)	3619 (7.6)	2385 (9.3)	2756 (5.8)	<.0001
Coronary heart disease <i>n</i> (%)	1666 (3.5)	1189 (4.7)	598 (2.7)	<.0001
Malignancy <i>n</i> (%)	1364 (2.9)	951 (3.7)	483 (2.2)	<.0001
Myocardial infarction <i>n</i> (%)	664 (1.4)	474 (1.9)	227 (1.1)	<.0001
Atrial fibrillation <i>n</i> (%)	571 (1.2)	419 (1.6)	238 (1.1)	<.0001
Stroke <i>n</i> (%)	566 (1.2)	395 (1.6)	206 (0.9)	<.0001
Valvular disease <sup>a</sup> <i>n</i> (%)	505 (1.1)	327 (1.3)	206 (0.9)	0.0004
Cardiomyopathy <i>n</i> (%)	71 (0.15)	53 (0.2)	22 (0.1)	0.0026

SD= standard deviation. p=.05

<sup>a</sup> Congenital heart disease and valve disease

\* Pearson Chi Square test for mean differences

**Table 2. Incidence rates for heart failure in patients with obesity who did and did not undergo bariatric surgery, by age group**

	Number at risk		Number of incident cases		Person-years		Incidence rate (95 % CI)*	
	Non-surgical	Surgical	Non-surgical	Surgical	Non-surgical	Surgical	Non-surgical	Surgical
All	25,564	22,295	944	89	137251	86008	6.9 (6.4-7.3)	1.0 (0.8-1.3)
Age groups								
18-44	13,139	14,349	105	16	71016	57844.3	1.5 (1.2-1.8)	0.3 (0.1-0.4)
45-49	3109	3095	77	19	16045.2	11063.4	4.8 (3.7-5.9)	1.7 (1.0-2.5)
50-54	2830	2246	104	18	15329	8228.5	6.8 (5.5-8.1)	2.2 (1.2-3.2)
55-59	2786	1694	182	14	16195.9	6017.5	11.2 (9.6-12.9)	2.3 (1.1-3.6)
60-64	2053	750	204	17	10640.5	2356.6	19.2 (16.5-21.8)	7.2 (3.8-10.6)
65-69	1095	152	162	5	5267.6	470.5	30.8 (26.0-35.5)	10.6 (1.3-19.9)
70-74	552	9	110	0	2756.7	27	39.9 (32.5-	0.0



							47.4)	
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CI=Confidence intervals.

\* per 1000 years.

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